REMARKS

The Applicants request entry of these amendments and reconsideration and withdrawal of the restriction requirement and the claim rejections in view of the following remarks.

I. INTRODUCTION

The present application has been assigned for examination to Group Art Unit 1649, a group that examines applications directed to inventions involving "Receptors, Cytokines & Recombinant Hormones, Neurobiology and Neuroimmunology." The present invention is none of those things.

The present invention relates generally to prions, a group of proteins that can exist in a soluble conformation as well as in an aggregated state *in vivo*. Aggregation of prions causes phenotypic changes to yeast, and neurological diseases in mammals. As explained at page 5 of the application, before the present application, there had been significant investigation into the biology of mammalian prions and prion-like yeast proteins for the purposes of developing a basic understanding of prion biology and developing effective measures for diagnosing, treating, and preventing mammalian prion diseases. However, until this application, industrial applications for prion and prion-like gene and proteins were lacking.

The present invention is believed to be the first invention directed to employing unique features of prion biology in a practical context beyond fundamental prion research and applied research directed to the development of diagnostic, therapeutic, and prophylactic treatments of mammalian prion diseases (although aspects of the invention have utility in such contexts also). More particularly, the present inventors have harnessed the fiber-forming properties of prions, and the extreme durability of those fibers, and the ability to modify those fibers, to provide nanotechnology solutions to a wide range of problems. The "elected species" is a yeast prion with no known involvement in mammalian neurological diseases.

Because the invention relates to molecules that form useful polymer fibers, it is proper to think about polypeptides of the invention in terms of their ability to form useful and durable fibers, preferably fibers that can be modified (e.g., at engineered reactive sites) to attach other functionalities. As explained in detail below,

the properties of prion proteins that cause such proteins to aggregate into fibers are quite different than the properties of receptors, cytokines, and hormones that permit them to interact highly specifically with their unique binding partners to exert downstream biological effects. Even though the current claim set has been assigned to a receptor/cytokine/hormone examining group, the applicants request that examination proceed based on the body of knowledge that exists concerning prion biology, and not on the body of knowledge or case law that is concerned with cytokine biology.

II. EXPLANATION OF AMENDMENTS

A. Amendments to the claims

Certain claims have been canceled solely to reduce fees for excess claims, in view of the newly added claims. Certain claims have been amended to correct obvious typographical errors. Certain claims have been narrowed to focus on genera that more closely relate to the applicants' election. None of the claim amendments are for reasons relating to patentability, and the applicants reserve the right to pursue claims to original subject matter in related applications, such as continuing applications.

The new claims find support in claims as previously filed, as well as throughout the specification, including at pages 8-11 and 17.

B. Amendments to the sequence listing and specification

One amendment corrects an obvious typographical error.

The applicants have determined that there were sequences in the figures that lacked sequence entries in the sequence listing. The sequence listing has been amended to introduce such sequences, which find support in the figures as

originally filed. The specification has been amended so that references to the relevant figures include cross-references to the sequence listing.[1]

Also shown in Figure 3 are sequences that are encoded by bases 418 to 1217 of SEQ ID NO: 49, which is set forth in SEQ ID NO: 68; bases 928 to 457 of SEQ ID NO: 49, which is set forth in SEQ ID NO: 69; and bases 7688 to 6933 of SEQ ID NO: 49, which is set forth in SEQ ID NO: 70.

III. TRAVERSAL OF RESTRICTION

In response to the most recent (third) restriction requirement, the Applicants previously elected Group VII (claims 121-123, 139 and 144), drawn to polypeptides having a SCHAG amino acid sequence. The Applicants further elected a "molecular embodiment": *S. cerevisiae* Sup35 polynucleotides and polypeptides (SEQ ID NO:2), and more particularly the NM regions (residues 1-253) and still more particularly the N region (amino acids 1-123) of this sequence. To the extent that a single modification was required, the Applicants elected substitution of a cysteine residue into the Sup35 sequence. To the extent that election of a single location was required, the Applicants elected a cysteine substitution at amino acid position 2.

The restriction was not made final. It is still improper, and should be withdrawn.

A. Response to particular issues raised in the Office action.

At page 3, the Examiner asserted, "the record is clear that the previous search and examination based upon previous restriction was limited to the extent of SEQ ID NO: 2 and cysteine substitutions . . . ." In fact, it is clear from the earlier prosecution history that the Examiner was considering both genus and species claims, consistent with the direction provided in the MPEP for examining generic claims in the context of a forced election of species. In contrast, the generic claims in the

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[1] The applicants also have determined that certain sequence entries identified at pages 62-63 of the specification and set forth in the sequence listing (SEQ ID NOs: 22, 24-25, 31-36) do not correspond identically to sequences in Genbank that are cross-referenced in the application. The Applicants reserve the right to amend the sequence listing to add sequences of the Genbank entries as filed. However, for the purposes of the elected claim set involving the Sup35 sequence, the issue is believed to be moot because Sup35 is not one of the affected sequences.

current office action have, improperly, been withdrawn from consideration, even though they encompass the elected subject matter.

The examiner also observe that it is not clear whether any polypeptides share the higher order composites as separately claimed. The evidence cited below demonstrates that Sup35 and Ure2 variants, including variants that have been "randomized" in terms of sequence, nonetheless form prion higher ordered structures.

The examiner expresses uncertainty about the relative scope of polymers, fibers, or filaments, and suggests that uncertainty is a basis for restriction. To the contrary, it is the PTO's burden to set forth a basis for restriction – not the applicants burden to demonstrate restriction is improper. The examiner is correct that a distinction has been made between aggregates that are not higher ordered aggregates (as defined in the application) and polymers/fibers/filaments that are ordered aggregates. That part of the prosecution history does not justify an as yet undefined restriction between forms of higher ordered aggregates.

Finally, the Applicants wish to point out that, to the extent an election of a particular substitution species was required, the applicants elected substitution at position 2 of SEQ ID NO: 2. The examiner appears to have improperly withdrawn such claims from consideration.

B. No substantial burden on PTO; fairness to applicants

The extensive prosecution history of this application demonstrates that examination of the entire current claim set is not a serious burden on the PTO. The previous examiner already has demonstrated that search and examination of the entire application, with claims directed to polypeptides and fibers/polymers, can be made without serious burden. Accordingly, the restriction is improper, and should be withdrawn. See MPEP 803 ("If the search and examination of an entire application can be made without serious burden, the examiner **must** examine it on the merits, even though it includes claims to independent or distinct inventions.") (Emphasis added.)

C. No burden with respect to SEQ ID NO:2 and substitutions

To the extent that the Applicants are restricted to pursuing claims limited to a yeast prion sequence or more specifically, to claims related to SEQ ID NO:2, there will be no serious burden to examining claims that embrace substitutions

at more than one elected residue. The first Examiner, who already examined generic claims, relied on a substituted amyloid beta prior art document as the motivation to substitute, and this reference has been distinguished by the Applicants. Moreover, the first Examiner deemed claims 117 and 118 allowable, and claims 117 and 118 encompass two different substitutions in SEQ ID NO:2 - amino acid position 184 in claim 117 and amino acid position 2 in claim 118. The existing claim set as well as the new claims currently include claims that are generic to more than one possible substitution in SEQ ID NO: 2.

D. Failure to identify characteristics that define the restriction groups

The Applicants reiterate their objection, set forth in detail in their traversal of the restrictin, that the Patent Office has wholly failed to explain what characteristics distinguish one polypeptide group from another; or one fiber group from another; or one polymer group from another; or a fiber group from a polymer group. This abbreviated method of issuing a restriction requirement ignores the MPEP-directed practice of "identifying each separate subject amongst which restriction is required, and grouping each claim with its subject." (MPEP 814.) If the restriction is maintained, the applicants request that the reasons be further articulated to give a fair opportunity to respond.

E. The restriction of fiber/polymer claims into eight separate restriction groups I-V and IX-XI was improper.

Notwithstanding a few boilerplate statements about "divergent structure" and "different effects" that might be alleged by any examiner in any generic restriction requirement, the Patent Office has failed to articulate any basis for restricting claims directed to fibers/polymers into eight distinct groups (or nine groups if Group VI is included).

In fact, a fiber/polymer comprised of the originally elected species, a yeast SEQ ID NO: 2 prion with a cysteine substitution with a metal atom substituent, falls within virtually every one of the allegedly distinct groups.[2] A restriction

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[2] Group III requires two reactive side chains and would not read on a species having only one such side chain. But, several claims in other groups specify "at least one" reactive side chain and, therefore, overlap in scope with Group III.

requirement in which one species falls within every restriction group is improper on its face, because a species cannot be independent or distinct from itself.

F. The restriction of polypeptide claims into three separate restriction groups VI-VIII was improper.

The arguments in Part B are applicable to the three alleged polypeptide restriction groups as well. A polypeptide comprising SEQ ID NO: 2 SCHAG sequence with a cysteine substitution (generically, as originally elected) falls within all three groups. A polypeptide comprising SEQ ID NO: 2 with a cysteine modifications at position 184 would fall within Groups VI and VIII. A polypeptide comprising SEQ ID NO: 2 with a cysteine modification at positions 2 and 184 would fall within Groups VII and VIII. As noted above, Group VI includes a claim directed to a polymer, and therefore would overlap with multiple members of the eight "polymer/fiber" groups. A restriction group cannot define an independent and distinct group when it overlaps with another group.

G. The requirement to "delineate the molecular embodiments to which the claims will be restricted" is improper.

The MPEP identifies certain circumstances in which an examiner may require an applicant to *elect a species* of invention, to which the claims may be restricted *if no generic claim is allowed.* However, the Examiner has specifically required an election of a "molecular embodiment" and asserted that such election is NOT a species election, and indicated an intention to refuse to examine generic claims. ("The subject matter for examination will be restricted to the extent of the subject matter elected.") The Applicants request that the authority for such a restriction be identified or the "molecular embodiment" restriction be withdrawn. The molecular embodiment restriction effectively turns what on its face is an eleven-way restriction, into a restriction of hundreds or thousands or millions of groups. The first examiner had no apparent difficulty examining the present application as originally filed based on a six-way restriction, and no valid basis exists for expanding it to thousands or millions of groups. Generic claims are permitted in every other

technology and there is no rule or statute prohibiting generic biotechnology inventions[3].

H. REQUEST FOR REJOINDER

Even if the restriction is maintained, the applicants request the opportunity to present (and have rejoined) fiber/polymer claims that depend from and are limited by polypeptide claims that may be deemed allowable.

IV. THE CLAIM OBJECTIONS SHOULD BE WITHDRAWN

In paragraph 8 of the Office action, the Examiner objected that the terms "glutamate" and "aspartate" were informal and asserted that "the art standard term for these amino acids is generally Glutamic Acid or Aspartic Acid . . . ." Because the application uses the former terms in the specification (see, e.g., p. 24) and original claims, the Applicants prefer not to amend the claims at this time. The Applicants agree that these are equivalent terms, but do not agree that one term is more standard or that either term is inappropriate. (See Exhibit H, excerpts from biotechnology dictionary, using both terms.) Accordingly, the objection should be withdrawn.

V. CLAIMS 121-123, 139, AND 144 AND RIGHT TO PRIORITY

In paragraph 9, the Examiner asserted that claims 121-123, 139, and 144 were not entitled to priority under §119(e), alleging that these claims "differ substantially from that disclosed within the provisional [application] and originally filed specification. In particular the peptides of claims 121-123 and 144 differ in composition and further the 'fibrous polymer' newly recited is not apparently disclosed." (Office action at 5-6.)

The Applicants reserve the right to dispute these allegations should they become material to patentability. However, priority is an appropriate issue for

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[3] In fact, the recent TC1600 Restriction Training for Examiners (August 2004) has numerous examples of structurally divergent molecules and other genera examined together in a single restriction group. (See, e.g., 1610/1620 Example 1 (emollients and humectants examined as a genus despite divergent structures) and Example 2 (chemical genus); and 1630/1640/1650 Example 1 (DNA and polypeptide genera)

ex parte examination only when an intervening reference that bears on patentability is an issue (MPEP 201.15), and that is not believed to be the case here. Unless these circumstances arise, the allegations regarding priority should be stricken.

VI. THE REJECTION FOR LACK OF WRITTEN DESCRIPTION SHOULD BE WITHDRAWN.

In paragraphs 11-12, the examiner rejected claims 121-123, 139, and 144, alleging lack of written description. The Applicants traverse.

A. Descriptive support for "fibrous polymer"

In paragraph 11, the examiner alleged that the application fails to support claims to a "fibrous polymer." This is incorrect. The application teaches at page 10, lines 14-22, that the Sup35 protein aggregates into *fibers*. The application explicitly states at page 20, lines 5-9, that the prion fibril aggregates are an aspect of the invention. At page 25, lines 20-25, the making of polymers from SCHAG amino acid sequences is described as an aspect of the invention. At page 28, first full paragraph, the application explains that fibrils, fibers, filamentous structures, and polymers are all aspects of the invention. The term "polymer" is defined as including aggregates that may or may not be filamentous. However, it is clear from the same paragraph that filamentous structures are specifically contemplated as an aspect of the invention. See generally pages 28-31. Copious additional support for fibrous polymers is additionally found in the detailed description.

Exemplary descriptive support for other elements of the claims as previously presented is summarized in the following table:

Claim recitation	Exemplary support
144. A polypeptide comprising the SCHAG amino acid sequence of SEQ ID NO: 2 . . .	SEQ ID NO: 2; page 10, lines 14-25
. . . with the proviso that amino acid 184 of SEQ ID NO: 2 has been substituted for by an amino acid selected from the group consisting of cysteine, lysine, tyrosine, glutamate, aspartate, and arginine . . .	P. 23, line 25, to p. 24, line 8; p. 27, lines 18-22; Examples 9-10, pp. 85-92
. . . or comprising a fragment thereof that includes said substituted amino acid and that self-coalesces to form higher ordered aggregates.	P. 10, line 14, to p. 11, line 19; p. 7, line 10, to p. 9, line 20. See also original claim 11.

121. A polypeptide according to claim 144, wherein the polypeptide self-coalesces to form fibrous higher ordered aggregates.	Same as above plus p. 6, line 9, to p. 10, line 25.
122. A polypeptide according to claim 121, wherein amino acid 184 of SEQ ID NO: 2 is exposed to the environment in the fibrous higher ordered aggregates.	Examples 9-10, especially paragraph bridging pp. 91-92.
123. A polypeptide according to claim 122, wherein amino acid 184 of SEQ ID NO: 2 is substituted for by a cysteine or glutamate.	P. 23, line 25, to p. 24, line 8; p. 27, lines 18-22; Examples 9-10, pp. 85-92
139. (previously presented) A fibrous polymer comprising polypeptide subunits coalesced into a fibrous aggregates, wherein at least one of the polypeptide subunits comprises a polypeptide according to any one of claims 144-145	page 28, first full paragraph

B. Descriptive Basis for genus claims

In paragraph 12, the examiner rejected the same claims, alleging that the claims encompassed an unduly large genus of sequences, relative to the supporting disclosure in the application. The applicants traverse.

The application contains a robust disclosure in support of generic claims. A non-limiting list of putative SCHAG proteins is set forth at page 7 of the application.

The application explicitly contemplates genera of SCHAG molecules with defined sequence variation, relative to wild type sequences. (See pages 8-9 and 11, for example.)

The application also provides guidance for making structure-function predictions concerning SCHAG polypeptides. For instance, Example 9, part B, of the specification teaches techniques for making point mutants and screening them for SCHAG properties relevant to the claims. In addition, Example 3 of the Application teaches that more substantial mutants can be constructed while preserving fiber-forming properties. In particular, the Applicants showed that the fiber forming properties of Sup35 (SEQ ID NO: 2) could be manipulated in a predictable manner by

increasing or decreasing the number of PQGGYQQYN oligopeptide repeats that occur in the peptide. (See pp. 54-58.)

Importantly, the application provides guidance that the percentage of polar residues (particularly asparagine and glutamine) is important for prion fiber forming properties of a polypeptide. (See generally pp. 8-9; Example 5; and additional explanation below.) The Application contains guidance that conservative substitutions are less likely to alter SCHAG properties. (See, e.g., p. 8.) Thus, there are structural as well as "functional" teachings in the application relating to identification of SCHAG sequences.

The application describes assays for the identification of novel prion-like amyloidogenic sequences and experiments for screening the sequences to confirm prion-forming properties. For example, Example 5 of the present application describes procedures that involve screening protein sequence databases and probing polynucleotide libraries to identify sequences suspected of having fiber-forming capabilities. Moreover, Example 5 further teaches how to screen such sequences to confirm that the sequences represent/encode proteins having the ability to self-aggregate into fibers. Example 5 describes an aggregation assay using fusion proteins and an in vitro aggregation assay using chaperone protein. Example 8 provides a high throughput genetic screen for identifying peptides with prion fiber-forming properties. Thus, the application provides clear direction in relation to the claimed method step of identifying a SCHAG sequence.

Thus, the descriptive support for the Applicants' genus claims is abundant throughout the application.

C. It is improper to apply "enzyme/substrate" or "receptor/ligand" structure-function analysis to the present invention involving prion structure-function relationships.

The breadth issue also must be considered in the context of the "function" recited in the claims. In the biotechnology arts, especially involving cytokines and receptors, the protein "function" in a patent application is often that of an enzyme, receptor, or ligand, or other "biological activity" function. In these circumstances, some sequence alterations, notably non-conservative alterations in an active site, might disrupt such "function," e.g., by altering a critical active site or

binding site. The sometimes stringent examination criteria applied to protein inventions involving "biological activity" should not be applied to the present invention (even though the applicants believe that such criteria are satisfied here), because evidence suggests the coalescing properties of SCHAG proteins are *more permissive of sequence variation.*

The present application contains repeated guidance that SCHAG peptides preferably are rich in polar, uncharged residues (especially asparagines (N) and glutamine (Q), but also serine and tyrosine) and relatively low amounts of secondary structure in their soluble state, whereas the peptides can also adopt a beta sheet structure in connection with a polymerized state. (See, e.g., specification at p. 8, lines 29-31; p. 4, lines 7-9; p. 51, lines 12-14; p. 61, lines 8-14 and 26-31.) For example, whereas an average globular protein may have a Q + N amino acid content of about 8%, prion proteins such as those described in the application typically have a Q + N content in excess of 30%. [See Exhibit B to the amendment filed on July 13, 2004, providing amino acid content of Sup35 and Ure2, broken down by domains. The N region of each molecule is the polar-residue rich SCHAG/prion domain.]

At the same time, a typical globular protein will have approximately 26% charged residues (K,R,E,D), whereas in the typical prion domain, the K+R+E+D content is less than about 12%.

While satisfying these general guidelines as to amino acid content, the examples in the application, and numerous examples in nature, demonstrate that peptides with these properties are **quite permissive of primary sequence variation,** while still maintaining SCHAG properties.

Exhibit C to the amendment filed on July 13, 2004, is an alignment of the amino acid sequences of three yeast/fungal Sup35 proteins that are specifically taught in the application. In the Sup35 N region (i.e., the SCHAG/prion domain), sequence similarity between these proteins is comparatively low: (S. cerevisiae: C. albicans ~ 26%; S. cerevisiae: P.pinus ~ 31%; S. cerevisiae: P.pinus ~ 45%), whereas similarity in the C region, responsible for protein function in the unaggregated protein, remains significantly higher. (The C region is not necessary for SCHAG properties that are relevant to the present claims.).

Exhibit D to the amendment filed on July 13, 2004, is a schematic that graphically depicts in **color**[4] these amino acid enrichment patterns in eight different species of Sup35. Whereas sequences are diverse from an amino acid sequence alignment standpoint, i.e., comparing primary sequence, the character of the amino acids found in the sequences are similar, and generally follow the guidance provided in the application and summarized above.

Example 3 of the Application teaches that the fiber forming properties of Sup35 (SEQ ID NO: 2) could be manipulated in a predictable manner by increasing or decreasing the number of PQGGYQQYN oligopeptide repeats that occur in the peptide. (See pp. 54-58.) This data is readily contrasted with traditional structure-function analyses, where inserting or deleting segments of primary sequence might be expected to have detrimental effects on conformation or activity.

Collectively, this evidence shows that the present application teaches common structural features for SCHAG sequences, and also shows that undue experimentation is not required because of the nature of the claims and the permissiveness of SCHAG sequences to sequence alterations. The relevant "function" of SCHAG peptides of the present invention is self-aggregation to form useful fibers, and this function does not raise the typical primary-structure-function issues raised by many other biotechnology patent applications. The invention can be practiced with a high expectation of success, even if primary amino acid sequence is modified within the guidelines of the application.

D. Recent evidence indicates that SCHAG properties of SUP35 can be maintained even when the primary amino acid sequence is scrambled!

Recent studies published in prominent journals have reported evidence that Sup35 and Ure2, two yeast prions that are prominently described in the present application, can still self-aggregate into polymers even after the primary amino acid sequence is scrambled, and even if segments of Sup35 are omitted entirely.

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[4] The applicants invite the examiner to contact the undersigned attorney for a color copy of Exhibit D as filed, in the event that Exhibit D was scanned by the PTO in black and white.

In the *PNAS* article attached hereto as "Exhibit E" (Ross et al., "Primary sequence independence for prion formation," *Proc. Natl Acad Sci, 102(36)*: 12825-830 (2005), Reed Wickner's laboratory reported that the sequences of the Sup35 prion domain can be "randomized" without blocking prion formation. The authors also reported, with respect to Ure2, that several tested fragments were able to form prions, and that no single sequence was found in all of the fragments. (P. 12827, col. 1) Based on their collective evidence, the authors conclude that prion aggregate formation was driven primarily by the *amino acid composition, rather than by sequence*. The authors also concluded that "length may be the primary determinant of inducing ability, with [Ure2] fragments longer than ~50-60 amino acids consistently inducing well and shorther fragments failing to induce." (p. 12826, col. 2.)

In an earlier study, the same research group showed that the amino acids of the Ure2 prion domain could be randomly shuffled, yet the resultant proteins still formed amyloid fibers *in vitro*. (See Exhibit F, Ross *et al.*, "Scrambled Prion Domains Form Prions and Amyloid," *Mol. Cell. Biol., 24(16)*; 7206-13 (2004)).

A recent publication from inventor Lindquist's laboratory summarizes work in which thirty-seven different cysteine-substitution mutations were introduced throughout the NM (prion) portion of Sup35, and all thirty-seven retained capacity to support a prion phenotype in yeast. (See Exhibit G, Krishnan & Lindquist, *Nature, 435*: 765-772 (2005).

Collectively, this additional data demonstrates that the fiber-forming properties of prions, including Sup35, is a robust property that can withstand drastic alterations in sequence. Thus, the disclosure in the present application properly supports genus claims, and concerns about unpredictability are misplaced.

E. Documents cited by the Patent Office support, rather than negate, patentability.

At page 9 of the action, the Patent Office expressed concern that protein aggregation was dependent on a number of factors, and cited a number of literature documents in support. The concern is misplaced.

The present application teaches conditions under which aggregation will occur. The existence of a body of literature that provides additional insight into other conditions that may favor or disfavor aggregation adds to the body of

knowledge of a person skilled in the art, but does not detract from the working teachings in the application. If anything, the other literature enhances the ability of a person of ordinary skill to form fibers as taught in the application.

F. Conclusion

For all of these reasons, the rejection for lack of written description was improper, and should be withdrawn.

VII. THE REJECTION FOR LACK OF ENABLING DISCLOSURE SHOULD BE WITHDRAWN

In paragraph 13 of the Office action, the Patent Office rejected claims 121-123, 139, and 144 under 35 USC §112, first paragraph, alleging lack of enabling disclosure. The applicants traverse.

This rejection is similar to the "written description" rejection insofar as the Patent Office is questioning whether the scope of the claims is commensurate with the teachings. The Patent Office acknowledges that the application is "enabling for aggregation as analyzed via spectroscopy and EM as exemplified throughout pp. 44-92 of the specification." However, the Patent Office worries that the teachings concerning "experimental variables" that relate to experimental conditions and amino acid sequences create an "undue experimentation" situation.

All of these concerns are fully addressed in the preceding section. The examiner's concerns relating to hypothetical conditions under which fibers might not form are irrelevant, because the applicants have taught conditions under which fibers can be formed. (In the context of the current *product* claims, nothing more can be required.) The applicants have pointed to abundant teachings in the application concerning how to make and test sequence variants. The applicants have pointed to guidance in the application concerning desirable amino acid content (e.g., relative abundance of polar uncharged residues, relative scarcity of charged residues) in sequence variant molecules. The applicants have provided direct evidence that the sequence of Sup35 or Ure2 can be altered, deleted, or even scrambled, while preserving fiber forming properties of the molecules.

Collectively, the specification and evidence shows a reasonable expectation of success with only routine experimentation. Thus, the rejection should be withdrawn.

VIII. THE REJECTIONS FOR INDEFINITENESS SHOULD BE WITHDRAWN

In paragraphs 14-15 of the Office action, the Examiner rejected claims 121-123, 139, and 144, alleging that the terms "higher ordered aggregates" and "fibrous polymer" were relative terms which render the claims indefinite. The applicants respectfully traverse.

Descriptive support for fibrous polymer is discussed above in part A of the remarks relating to written description. One of ordinary skill in the art has no difficulty looking at a structure and concluding whether or not it is fibrous in appearance or structure. Accordingly, the rejection should be withdrawn.

The application provides guidance on the meaning of "higher ordered aggregates" at page 6, lines 14-19, for example. There, the application explains that higher ordered aggregates have at least 25 polypeptide subunits. The term excludes oligomeric proteins and excludes random agglomerations of prorteins. Common properties of aggregates, such as rich beta-sheet structure, also are discussed throughout the application.

It is also clear from the literature in the field that a person of ordinary skill in the field has no difficulty distinguishing higher ordered aggregates of prion-like proteins from random agglomerations or other protein structures.

IX. THE REJECTION BASED ON PRIOR ART SHOULD BE WITHDRAWN.

In paragraph 18, the Examiner alleged that claims 121-123, 139, and 144 were anticipated by Kushnirov et al. (IDS C76). The Applicants respectfully traverse.

The applicants dispute the merits of the rejection, because the examiner has failed to identify all of the limitations of the claims in the cited reference. However, independent claim 144 has been amended to specify that the substitution at position 184 is a cysteine, rendering the rejection moot, because Kushnirov allegedly has a glutamatic acid at this position.

The examiner alleged that claims 121-123, 139, and 144 are anticipated by Wei et al. The Applicants respectfully traverse.

The Wei et al reference relates to a completely different protein (cystatin C) than SEQ ID NO: 2, the subject of the claims. At the outset, the Applicants observe that the examiner has failed to assert that cystatin C or any particular fragment thereof satisfies the structural limitations of claim 144, other than possibly a single amino acid fragment: "The polypeptides of the claims relate to single amino acid substitutions. Any of the residues of Cystatin C either in the variant or wild type form that are of cysteine, lysine, tyrosine, glutamic acid, aspartic acid or arginine are sufficient to qualify as polypeptides comprising suitable portions or fragment that form higher ordered aggretate and fibrous polymer structures as the peptides are noted to form amyloid fibrils." If the examiner is asserting that some portion of cystatin C (other than a single amino acid) anticipates the claims, then the Applicants request that the rejection be clarified to permit an opportunity to respond.

The allegation that a single amino acid from cystatin C or any other protein satisfies the claims is without support and without merit, and fails to form a prima facie case for an anticipation rejection. Even if, for the sake of argument, the reference taught single amino acid "peptides" as alleged by the examiner, the examiner nonetheless is relying on principles of inherency to assert that the aggregation properties recited in the claims are satisified. As summarized in MPEP 2112, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." (Emphasis in original) *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), *In re Oelrich*, 666 F.2d 578, 581-582, 212 USPQ 323, 326 CCPA 1981). Rather, "[t]o make or establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The

mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " (emphasis added) *In re Robertson*, 169 F.3d 743, 749, 49 49 USPQ2d 1949, 19502-51 (Fed. Cir. 1999).

The examiner herself does not even believe that this inherency standard is satisfied. For example, at pages 9-10 of the Office action, the examiner asserts that the skilled artisan would not expect similar structure amongst different sequences or different experimental conditions, and alleges that undue experimentation would be required to practice the invention. "Would not expect" can hardly be said to satisfy the "necessarily present" standard.

For all of these reasons, the rejections based on prior art should be withdrawn.

VI. CONCLUSION

For the foregoing reasons, the applicants request that the restriction and rejections be withdrawn and that the claims be allowed. If this response requires any fee or a petition for extension of time that has not been filed herewith, then please consider this a request for such extension of time and charge any fees due to charge Marshall, Gerstein & Borun, LLP, deposit account number 13-2855, under matter number 30554/34978A.

Respectfully submitted,

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